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Low risk of contrast media-induced acute renal failure in nonazotemic type 2 diabetes mellitus

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Diabetes mellitus afflicts about 10 million Americans and appears to be increasing at the rate of 6% per year. Bergman, Ellison, and Dunea [1] initially reported the occurrence of acute renal failure in a diabetic patient after infusion urography. Since that time, at least 122 insulin-dependent (type 1) and maturity onset (type 2) diabetic patients who developed deterioration of renal function after contrast media study have been reported [1–21]. Among these 122, 70 patients (57.3%) evidenced renal dysfunction following intravenous urography (IVU). Sixty-four (91%) of these 70 patients had a serum creatinine concentration equal to or more than 2 mg/dl, while six had a level below 2 mg/dl before receiving contrast media. Of the other 52 diabetic patients who developed renal failure following other contrast media studies [aortography, selective angiography, intravenous cholangiography, and CAT scanning] 12 (23%) had a serum creatinine concentration less than 2 mg/dl prior to the study. Thus, of 122 patients developing contrast media-induced renal failure, 18 (15%) had serum creatinine concentrations below 2 mg/dl. A serum creatinine concentration of 2 mg/dl was selected for analyzing prior reports to exclude minor creatinine elevations due to diuretics or transient dehydration.

To ascertain whether or not diabetic patients with apparent good renal function face an increased risk of renal dysfunction from exposure to contrast media, a prospective study was performed in 49 type 2 diabetic patients with serum creatinine less than 2 mg/dl who were to undergo IVU.

Methods

Patient population. The study included 49 randomly selected type 2 diabetic patients with a serum creatinine concentration below 2 mg/dl who were admitted to the Diabetic Research Hospital at the University of Alabama in Birmingham. Patients ranged in age from 38 to 82 years (mean, 62 ± 10 years). Twenty (40%) were below 60 years, and twenty-nine (60%) were over 60 years old. There were 19 men and 30 women. Fifteen patients had known of the diagnosis of diabetes mellitus for less than 5 years, while 16 had been diagnosed as diabetic for over 16 years. The mean age at diagnosis was 51 years (range, 35 to 73 years). Hypertension was noted in 38 (78%) patients; hypertensive patients had a mean systolic pressure of 175 ± 29 mm Hg and a mean diastolic pressure of 89 ± 19 mm Hg. All patients were admitted for a comprehensive appraisal of their diabetic status.

Informed consent was obtained from patients after thorough explanation of the objectives and risks of the study.

Study protocol. Day 1: A fasting venous blood sample was drawn for measurement of plasma glucose, serum creatinine, and uric acid. *Day 2:* A 24-hr urine specimen was collected, and an aliquot was taken for measurement of protein and creatinine. *Day 3:* In preparation for IVU, patients were not dehydrated or given a laxative, and were encouraged to drink water during the night. They were allowed to drink water after midnight. The IVU was performed in the morning, using 100 ml of sodium diatrizoate 29.1%, and meglumine diatrizoate 28.5% (Renovist II®). The dye was administered intravenously over several minutes.

Chemical testing of blood samples was performed on an autoanalyzer with less than 5% variation in repeat measurements of creatinine, urea nitrogen, and electrolytes. Serum creatinine measurements were repeated 1, 3, and 6 days after IVU. Deterioration of renal function was defined as a rise in the serum creatinine concentration of at least 25%, or 0.5 mg/dl, occurring within 48 hr after contrast media administration in the absence of sepsis, hypotension, or other potential causes of acute renal failure. A poststudy reduction in daily urinary output to 400 ml or more was regarded as oliguria.

Results

Of 49 patients studied, three (6%) had an elevation of serum creatinine concentration greater than 25% by day 3. One patient, a 67-year-old white man with a 32-year history of diabetes mellitus, developed oliguria on day 2; the oliguria lasted 2 days. His serum creatinine concentration rose from 1.1 mg/dl before IVU to 3.2 mg/dl by day 3. One week post-IVU, his serum creatinine fell to 1.9 mg/dl. Physical examination disclosed peripheral sensory neuropathy, but no retinopathy was detected on fluoroscein angiography. All other screening biochemical tests were within normal limits. His creatinine clearance was 74 ml/min, with only 29 mg of urinary protein per 24 hr. His BP was 174/100 mm Hg on the day of IVU study. The patient had been treated with insulin in the past, but for the last

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3 years, he had been managed by diet alone achieving "good" control of blood glucose concentration.

Post-IVU elevations in the serum creatinine concentration were observed in two other men below the age of 60, each with known diabetes for less than 5 years, within 3 days following IVU (1.3 to 2.1, 1.2 to 2.1 mg/dl, respectively). Neither man had a history of hypertension. Physical examination in these two men disclosed neither neuropathy nor retinopathy. All of their biochemical tests were within normal limits. Their creatinine clearances were 60 and 105 ml/min, respectively, prior to the IVU study.

A comparison of the patients with post-IVU azotemia and those without a serum creatinine rise is given in Table 1. Although the renal failure group, consisting of three subjects, is too small for statistical comparison, elevation in BP, uric acid, and urine protein occurred more frequently in those without evidence of renal dysfunction. The mean creatinine difference in serum samples drawn before IVU, and one to three days post-IVU in the three patients with renal dysfunction and the other 46 patients without renal dysfunction are shown in Tables 2 and 3. Most patients (37 and 39 of 46) whose serum creatinine concentrations were not elevated after IVU, had equal or lower serum creatinine concentrations on the first or third day post-IVU compared to their prestudy levels. All three with renal dysfunction after IVU had an elevation of serum creatinine on the first post-IVU day. The increase in serum creatinine was significant, $P < 0.01$ using the Fisher Exact Test.

Of 29 patients over age 60, 13 (45%) had a creatinine clearance of less than 70 ml/min (range, 36 to 69 ml/min), and none had increased serum creatinine concentrations following IVU. Of the 16 (55%) elderly patients who had a creatinine clearance over 70 ml/min (range, 70 to 194 ml/min), one developed acute oliguric renal failure, although he had a creatinine clearance of 74 ml/min before IVU.

In the group of 20 patients under age 60, only two (10%) had a creatinine clearance of less than 70 ml/min (45 and 60 ml/min, respectively). Of these "younger" diabetes mellitus patients, one developed renal dysfunction following IVU. He had a creatinine clearance of 60 ml/min before IVU. Considering the 18 (37%) patients with creatinine clearance over 70 ml/min (range, 70 to 106 ml/min), only one exhibited an increase of serum creatinine concentration after IVU. Proteinuria, defined as more than 150 mg/24 hr, was present in nine patients, eight of whom were hypertensive, and seven of whom were older than 68 years, but none developed post-IVU azotemia. The mean creatinine clearance of the proteinuric group was 79.7 ml/min (range, 60 to 99 ml/min).

The serum creatinine concentration returned to a prestudy level in all three patients who had shown a rise. None needed dialysis.

Table 1. Clinical and laboratory data of 49 type 2 diabetes mellitus studied by IVP

	Patients with renal dysfunction after IVP	Patients without renal dysfunction after IVP
Patient no.	3	46
Age, *years*	57 ± 11	63 ± 11
Sex, *male*	3	15
Onset of diabetes mellitus, *years of age*	45 ± 11	52 ± 1
Duration of diabetes mellitus, *years*	12 ± 17 (range, 1 to 32 years)	12 ± 8
Retinopathy	0	4
Neuropathy	1	23
Hypertension	1	37
Serum uric acid, *> 8 mg/dl*	0	8
Urine protein, *≥ 150 mg/24 hr*	0	9
Creatinine clearance, *ml/min*	79.6 ± 23 (range, 60 to 105)	76.5 ± 26 (range, 36 to 195)

Table 2. Comparison of mean serum creatinine concentration on first post-IVP day and pre-study level in 49 type 2 diabetes mellitus patients[a]

	Renal dysfunction post-IVP		
	Yes	No	*Total*
Δ Serum creatinine $\bar{P}$ 1 day vs. prestudy ≤0	0	37	*37*
Δ Serum creatinine $\bar{P}$ 1 day vs. prestudy >0	3	9	*12*
Total	*3*	*46*	*49*

[a] $P \leq 0.011$ with Fisher Exact Test.

Table 3. Comparison of serum creatinine concentration on third post-IVP day and pre-study level in 49 type 2 diabetes mellitus patients[a]

	Renal dysfunction post-IVP		
	Yes	No	*Total*
Δ Serum creatinine $\bar{P}$ 3 days vs. prestudy ≤ 0	0	39	*39*
Δ Serum creatinine $\bar{P}$ 3 days vs. prestudy > 0	3	7	*10*
Total	*3*	*46*	*49*

[a] $P \leq 0.006$ with Fisher Exact Test.

Discussion

In the present report, three of 49 (6%) type 2 diabetic patients developed renal dysfunction following intravenous urography despite an absence of dehydration prior to contrast media injection. Their serum creatinine concentrations were all below 1.3 mg/dl, and their creatinine clearance was above 60 ml/min before the study. Only one of these three became oliguric. After 2 days of oliguria a peak serum creatinine concentration of 3.2 mg/dl was noted on day 3 post-IVU. The serum creatinine concentration in this patient returned to prestudy level in 2 weeks. This patient, who had been diabetic for 30 years, had been hypertensive for more than 40 years, but no evidence of nephropathy or retinopathy was detected on physical examination. Only two other patients evinced mild elevation of serum creatinine (1.1 to 2.1 and 1.2 to 2.1 mg/dl, respectively) but did not become oliguric. Their serum creatinine concentrations returned to prestudy values within 1 week. No patient developed irreversible azotemia or oliguria.

Harkonen and Kjellstrand [20] reported four nonuremic diabetic patients who had an elevation of serum creatinine follow-

Table 4. Renal dysfunction following IVP in nonuremic diabetes mellitus patients

Age	Sex	Duration of diabetes mellitus *yr*	Serum creatinine, *mg/dl*			Potential risk factors	Iodine dosage *g*	Reference
			Before IVP	Maximal	Recovery			
57	F	10	1.9	5.5 Oliguria	4.7 × 3 days	BP, *200/85 mm Hg* Diabetic microangiopathy Urinary tract infection Repeat IVU in 1 week Dehydration	51.6	[12]
62	F	15	1.4	2.7 Oliguria	2.2 × 2 days	BP, *160/95 mm Hg* Diabetic microangiopathy Dehydration	0.3 g/kg	[6]
67	NA	NA	1.8	NA	NA	Hypertension Nephrolithiasis and unilateral obstruction Dehydration	42.3	[13]
81	NA	NA	1.5	NA	NA	BPH with retention Dehydration Diuretic and antibiotics before IVP	42.3	[13]
21	M	15	1.5	5.1	2.3	Diabetic microangiopathy Proteinuria, *1.2 g/24 hr* Creatinine clearance, *50 ml/min*	NA	[17]
NA	NA	NA	1.6	3.8	1.5	Juvenile onset diabetes with long duration (?)	18	[20]
67	M	32	1.1	3.2 Oliguria	1.9 × 2 days	BP, *174/100 mm Hg* Diabetic neuropathy	31	Present study

Abbreviations are: NA, not available; BPH, Benign prostatic hypertrophy.

ing IVU. Three of these four had proteinuria, and a serum creatinine concentration of 1.6 to 1.8 mg/dl before IVU. One of these patients developed transient acute oliguric renal failure. By contrast, none of our three patients had proteinuria, or prior renal failure, although one, age 46, had a creatinine clearance of 60 ml/min, indicating a mild degree of renal insufficiency. The diagnosis of type 2 diabetes mellitus in these three patients is substantiated by their regulation without insulin treatment, and C-peptide values within normal limits.

Long duration diabetes mellitus has been proposed as a risk factor for renal dysfunction following contrast media study [15]. Although two of the three patients had overt diabetes mellitus for less than 5 years, it is not known whether or not these patients had earlier undetected diabetes mellitus. The precise timing of the onset of type 2 diabetes mellitus is often impossible. Previous reports refer to six diabetic patients who had post-contrast media renal failure and whose serum creatinine level was below 2 mg/dl [6, 12, 13, 17, 20]. At least three risk factors might explain the occurrence, albeit rare, of acute renal failure following IVU in diabetic patients with apparently normal renal function prior to exposure to contrast media (Table 4). The first relates to known abnormalities in diabetes mellitus. Diabetic patients have high blood viscosity [22–26], which is greatest in poorly controlled diabetes mellitus [23]. Hyperviscosity can promote blood stasis in capillary and postcapillary venules [27–29]. Reduced blood flow in postcapillary venules may lead to hypoxia, favoring formation of microthrombi [27, 28]. Blood viscosity may be further increased by dehydration [23] or infusion of hyperosmolar substances [30], including contrast media. Fajers and Gelin [31] demonstrated that red cell aggregation following intravenous administration of an hyperosmolar substance can cause necrosis of proximal tubular cells. Following an injection of currently used contrast media, such as diatrizoate, there may be a flattening and distortion in the shape of red blood cells, changes which can increase blood viscosity and can slow blood flow in postcapillary venules, causing renal ischemia [32].

In small vessels, through which red cells pass in single file, such as the afferent and efferent glomerular arterioles, erythrocytes must normally bend and deform in passage [33]. In diabetes mellitus, erythrocyte deformability is reduced [22]. This impaired deformability can result in blood flow reduction in the microcirculation causing renal ischemia. Erythrocyte deformability is restricted further following infusion of contrast media [34, 35].

Abnormal platelet aggregation [36, 37], might contribute to the genesis of diabetic macro and microangiopathy [38]. Contrast media have been reported to reduce platelet aggregation [39] while inhibiting clotting factors [40]. Recently, however, Peterson and Gormsen [41] found no significant difference in platelet aggregation between normal control persons and diabetic patients.

Arteriosclerosis of afferent and efferent glomerular vessels could predispose to renal injury. Diffuse arterial intimal fibrosis

Table 5. Possible risk factors in non-uremic diabetes mellitus patients who developed renal failure following intravenous pyelography (IVP)

A. Primary underlying abnormalities:
1. Abnormal rheology
a. Hyperviscosity
b. Reduced deformability of red blood cell
c. Increased platelet aggregation
2. Diabetic artheriosclerosis and glomerulosclerosis
B. Contrast media-induced abnormalities:
a. Acute rheologic changes
b. Acute hemodynamic changes
c. Direct tubular toxicity
C. Secondary predisposing factors:
a. Dehydration
b. Hypertension
c. Repeated IVP in short period

is almost universal in diabetic patients after age 50 [42]. Mogensen [43] reported that 83% of diabetic patients have hyalinization of renal arterioles and interstitial fibrosis. Although GFR is supranormal in type 1 diabetes mellitus [43], once either constant proteinuria, or hypertensive arteriosclerosis develops, renal blood flow declines [40, 44, 45]. Superimposition of dehydration [46, 47] can reduce further renal cortical blood flow accentuating renal ischemia, which, in turn, may lead to acute tubular necrosis [48].

Evidence supporting the direct toxicity of contrast media to renal tubules has been presented by Goldstein et al [49] who demonstrated the presence of glutathione S-transferase (ligandin) in the urine samples of certain patients following renal angiography. Soby and Hoy [50] also found a 50% decrease in para-aminohippurate extraction in 20 consecutive patients undergoing renal angiography, an observation confirmed by Danford, Talner, and Davidson [51] in dogs. Gup et al [52] reported decreased renal blood flow in three of ten nondiabetic patients with normal renal function and filtration rate. Renal blood flow fell in five of ten patients following intravenous administration of 1 ml of 50% sodium diatrizoate per pound of body weight. The effect of a similar dose of contrast media in diabetes mellitus patients has not been studied.

Dehydration decreases cortical blood flow and increases blood viscosity [46, 47]. Acute renal failure occurs more frequently in patients dehydrated before IVU [5, 48]. Adequate hydration does not always prevent acute renal failure [3, 6], as shown in this study's patients.

Therefore, it is difficult to propose a specific level of renal function at which procedures requiring administration of contrast media might be considered safe in diabetes mellitus patients. This study of type 2 diabetes mellitus did not discern a supranormal GFR (measured by endogenous creatinine clearance) in either short- or long-term patients (unpublished data). The absolute risk of an IVU in a type 2 diabetic patient who is neither dehydrated nor azotemic is probably small. In this study, 8 of 16 patients who had diabetes mellitus for longer than 15 years with reduced creatinine clearances below 70 ml/min (range, 36 to 69 ml/min), withstood IVU without subsequent azotemia or oliguria (Table 4). As a first guideline, it might be suggested that type 2 diabetic patients with creatinine clearances greater than 35 ml/min can be subjected safely to the amount of contrast medium given in IVU, providing they do not have other concomitant abnormality, such as proteinuria greater than 2 g/24 hr. Repeated contrast medium exposure may pose a cumulative risk if performed over several days [12].

In conclusion, contrast medium administration for intravenous urography in type 2 diabetes mellitus will induce reversible renal dysfunction in 6% of patients whose serum creatinine concentration is below 2 mg/dl. IVU in a well hydrated nonazotemic diabetic patient is considered to be safe. The pathogenesis of the small incidence of acute renal failure in this subset of diabetics is unknown but may be related to basic underlying abnormalities of diabetes mellitus, advanced age, dehydration, arteriosclerosis, and the subsequent alteration of blood viscosity induced by hyperosmolar contrast media [53].

Summary. The risk of developing contrast media-induced acute renal failure was studied in 49 randomly selected nonazotemic type 2 adult diabetic patients subjected to IVU. There were 19 men and 30 women in the group whose mean age was 62 ± 10 years (range, 38 to 82 years). In preparation for IVU, patients were neither dehydrated nor given a laxative. The IVU was performed in the morning, using sodium diatrizoate and meglumine diatrizoate. Serum creatinine levels were measured pre-IVU and on days 1, 3, and 6 after the IVU. A total of three patients (6%) had an elevation of serum creatinine greater than 25% above the baseline by post-IVU day 3. One patient developed oliguria (<400 ml/24 hr) that lasted 2 days. Creatinine clearances of the three patients showing contrast media toxicity were 74, 60, and 105 ml/min pre-IVU. In each of the three patients, a return to pre-IVU serum creatinine concentration was noted within 2 weeks. It is concluded that the risk of acute renal failure post-IVU is small in hydrated nonazotemic type 2 diabetic patients.

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